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14. ABSTRACT

Metastasis, a process during which primary tumor disseminates into distal sites, likely occurs when primary tumor cells obtain additional genetic or epigenetic alteration. ERBP (estrogen receptor binding protein) is an estrogen receptor binding protein which potentiates the transcriptional activity of estrogen receptor. Unlike most coactivators which interact with AF2 domain of estrogen receptor, ERBP interacts with the DNA binding domain of estrogen receptor. The altered expression of ERBP could promote the metastasis through enhancing the expression of genes which are regulated by estrogen and are involved in the breast cancer metastasis. By overexpressing ERBP in breast cancer cells, we found ERBP overexpression enhanced the migration and invasion capability of tumor cells. ERBP overexpression also promoted the tumor formation in nude mice. We identified 8 estrogen inducible genes which were up-regulated by ERBP overexpression. Finally, we found that expression of ERBP is increased in about 30% of breast cancers

15. SUBJECT TERMS
Breast carcinoma; metastasis; estrogen receptor.

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Table of Contents

INTRODUCTION

Metastasis, a process during which primary tumor disseminates into distal sites, likely occurs when primary tumor cells obtain additional genetic or epigenetic alteration. ERBP (estrogen receptor binding protein) is an estrogen receptor binding protein which potentiates the transcriptional activity of estrogen receptor. Unlike most coactivators which interact with AF2 domain of estrogen receptor, ERBP interacts with the DNA binding domain of estrogen receptor. Recently, we found that the expression of ERBP was dramatically increased when ER positive breast cancer MCF-7 cells acquire the capability of metastasizing. The proposed studies tested the hypothesis that the acquisition of ERBP overexpression promotes the metastasis through enhancing the expression of genes which are regulated by estrogen and are involved in the breast cancer metastasis.

BODY

Task 1. To determine if overexpression of ERBP promotes tumor metastasis.
By overexpressing ERBP in breast cancer cell MCF-7, we found ERBP overexpression enhanced the migration (Fig. 1A) and invasion capability (Fig. 1B) of tumor cells. ERBP overexpression also promoted the tumor formation in nude mice (Fig. 2). But no metastasis into lung was detected for both tumor cells overexpressing ERBP and control cells.

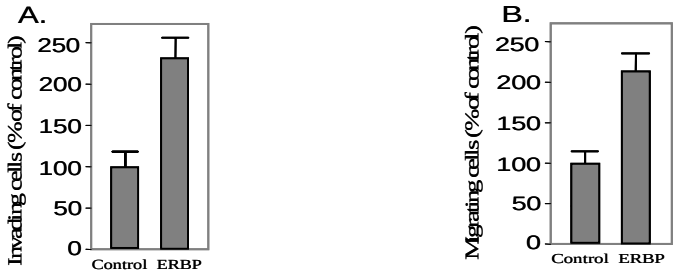
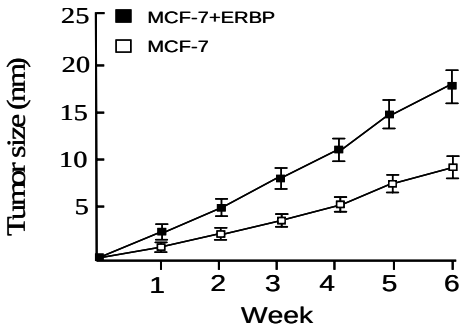


Fig. 1. A). Overexpression of ERBP increased the migration of MCF-7 cells through polycarbonate Transwell filters. B). Overexpression of ERBP enhanced the invasion of MCT-7 cells to the bottom layers of the Matrigel-coated membranes. Data represent the average of three independent experiments.

Fig. 2. The curve of tumor growth in nude mice. Two clones of MCF-7 cells or two clones of MCF-7 cells overexpressing ERBP ($1X10^6$ cells from each clone) were injected into nude mice, respectively. The experiment was performed in triplicate and the average tumor sizes were calculated.



Task 2. To identify the estrogen responsive genes regulated by ERBP.
We identified 8 estrogen inducible genes (Table 1) which were up-regulated by ERBP overexpression.

Table 1. List of estrogen responsive genes up-regulated by ERBP

GeneBank No.	Gene Name	Fold
NM_003881	WISP-2	2.0
NM_003225	TFF1	2.1
NM_001657	Amphiregulin	2.2
AF245389	Greb1	2.2
NM_003489	NRIP1	2.3
NM_000926	Progesterone Receptor	2.5
NM_005080	XBP-1	2.8
NM_000820	GAS6	3.1

Task 3. To determine if ERBP expression is increased in metastatic breast cancers in comparison with primary breast cancers.
We found that expression of ERBP is increased in about 30% of breast cancers (Fig. 3). We did not see ERBP expression was increased in metastatic tumors.

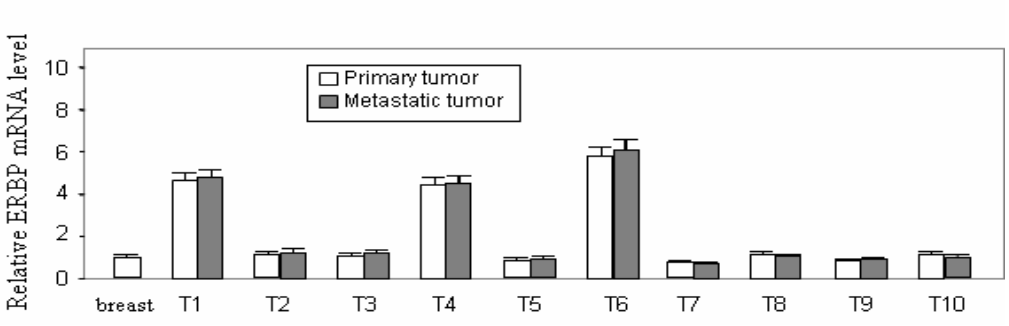


Fig. 3. ERBP expression was increased in about 30% of breast cancers. Tumor T1, T4 and T6 showed increased expression of ERBP with similar levels of expression in primary and metastatic tumors.

KEY RESEARCH ACCOMPLISHMENTS

* We found ERBP overexpression enhanced the migration and invasion capability of tumor cells. ERBP overexpression also promoted the tumor formation in nude mice.

* We identified 8 estrogen inducible genes which were up-regulated by ERBP overexpression.

* We found that expression of ERBP is increased in about 30% of breast cancers.

REPORTABLE OUTCOMES

None

CONCLUSIONS

ERBP overexpression enhanced the migration and invasion capability of tumor cells and the tumor formation in nude mice. Expression of ERBP is increased in about 30% of breast cancers.

REFERENCES

None

APPENDICES

None.